Remarks

In the Office Action dated November 16, 2004, claims 1-17, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-17 remain in this application.

The title was objected to as not descriptive. The original title has been deleted and the title suggested by the examiner has been added to the application. In view of this, applicants request that this objection be withdrawn.

Claims 6 and 13 were objected to due to clerical errors. Claims 6 and 13 have been amended as suggested in the office action. In view of these amendments, applicants request that this objection be withdrawn.

Claims 1-17 were rejected under 35 USC §103(a) as unpatentable over Pentapharm product catalog, Xing, De Vita and Medenica. Pentapharm discloses Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(L)-phenylalanine 4-ethoxycarbonylpiperazide as a urokinase inhibitor but does not disclose a racemate or D- enantiomers. In the Pentapharm Product Catalog the compound triisopropylphenylsulfonyl-3-amidino-(L)-phenylalanine-4-ethoxycarbonyl-piperazide (WX-UK1) is offered only as a chemical product for research, more precisely for research, analytical uses and purification processes. The Pentapharm Product Catalog features a separate chapter disclosing "pharmaceutically effective substances",

however, WX-UK1 is not offered as a pharmaceutically effective substance. Thus, contrary to the statements in the office action, Pentapharm has not produced and offered a composition containing WX-UK1 as a prospective pharmaceutical. Since the Pentapharm product is a chemical product for research, Pentapharm does not suggest or disclose a method for inhibiting the growth and spreading of malignant tumors, metastases and lung foci by administering the claimed compound. Xing is cited for the disclosure of using a urokinase inhibitor to prevent breast cancer growth, invasion and metastasis. However, Xing tested only the administration of Tamoxifen alone or in combination with the urokinase inhibitor B-428. The urokinase inhibitor B-428 is not structurally similar to the presently claimed urokinase inhibitor. Applicants point out that not all urokinase inhibitors per se are applicable as anticancer drugs. As is known to every person skilled in the art, substances to be used as therapeutics have to fulfill certain requirements with regard to pharmacokinetics and dynamics performance, and biodistribution must be considered as well. This is not predictable and can only be determined after performing *in vivo* experiments. Only when *in vivo* experiments are successful can the prospective therapeutic be clinically developed further. Thus, it cannot be inferred from the disclosure of Xing et al. (which only relates to the substance B-428) that all urokinase inhibitors can be used as medicaments for inhibiting the growth and spreading of malignant tumors, metastases and lung foci. Therefore, applicants contend that Xing does not cure the above discussed deficiencies in Pentapharm.

De Vita was cited for the general disclosure that carcinomas spread and grow in the lymphatic system and that UPA contributes to tumor cell invasion. Medenica was cited for the disclosure of chemotherapeutic or cytotoxic drugs.

Applicants respectfully point out that the compound Tamoxifen disclosed in Xing et al. is an antiestrogen and not a cytotoxic substance. The mechanism of action of this antiestrogen involves reduced tumor growth due to the accordant antihormone effect of the Tamoxifen, and is not based on a cytotoxic effect. In contrast thereto, cytotoxic agents are cell toxins, i.e. substances causing cellular death. Antihormones do not function cytotoxically and do not lead to cellular death. They reduce cellular and growth-significant information pathways and thus reduce hormone-induced cell growth. Due to this mechanism of action, Tamoxifen can be used only in tumours containing estrogen receptor. The fact that Tamoxifen is not a cytotoxic agent has been known for a long time. Enclosed is an excerpt from the compandium "Onkologie" as well as excerpts from the web page "Breastcancer.org" (a page containing information regarding breast cancer) and from "Cancer Facts", the online information portal of the National Cancer Institute, USA which indicate that Tamoxifen is not a cytotoxic agent. In view of this, applicants contend that one skilled in the art would not combine a different urokinase inhibitor with a cytotoxic agent to arrive at the present invention in view of the cited references.

The present invention reduces the primary tumour because of the cytotoxic component of the combination preparation. At the same time the present invention prevents the formation of metastases by using a urokinase inhibitor and/or enhances the effect of a monotherapy based on cytotoxic agents. Applicants point out that even

if the primary tumor has been reduced during the monotherapy by cytostatics, this effect is not extensive and the remaining tumor cells still possess the ability to spread and to form lethal metastases. Clearly it is imperative to prevent such metastases.

In view of the above discussion, applicants respectfully contend that the combination of Pentapharm, Xing, DeVita and Medenica does not suggest or disclose a method for inhibiting the growth and/or spreading of malignant tumors, metastases and/or lung foci, comprising administering a composition comprising Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, the L enantiomer thereof or a pharmaceutically suitable salt thereof. The only cited reference which discloses Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide is Pentapharm which discloses the compound as a research chemical not a therapeutic agent. None of the remaining references cures this deficiency. In addition, Xing discloses only that a single urokinase inhibitor B-428 can be used as a medicament for inhibiting the growth and spreading of malignant tumors, metastases and lung foci. Xing's urokinase is structurally different from urokinase inhibitor of the present invention and thus one could not reasonably conclude that the urokinase inhibitor of the present invention would have the same properties as B-428. De Vita teaches that carcinomas spread and grow in the lymphatic system and that UPA contributes to tumor cell invasion but does not suggest that any and all urokinase inhibitors will inhibit the growth and spreading of malignant tumors, metastases and lung foci. Medenica discloses chemotherapeutic or cytotoxic drugs but none of the cited references suggest or disclose that cytotoxic drugs should be combined with Nα(2,4,6-

Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide which as discussed above was not used as a pharmaceutical agent at the time the present invention was made. In view of the above discussion, applicants request that these rejections be withdrawn.

Applicants respectfully submit that all of claims 1-17 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By 

Monica Chin Kitts
Attorney for Applicant
Registration No. 36,105
ROTHWELL, FIGG, ERNST & MANBECK
1425 K. Street, Suite 800
Washington, D.C. 20005
Telephone: (202) 783-6040

MCK/cb